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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/355,793	09/21/99	BLASER	M D5979

EXAMINER	
PORTNER, V	
ART UNIT	**PAPER NUMBER**
1641	6

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DATE MAILED: 04/27/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/355,793	Applicant(s) Blaser et al
	Examiner Portner	Group Art Unit 1641

☒ Responsive to communication(s) filed on *Sep 21, 1999* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-17* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-17* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☒ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-17 are pending.

Priority

1. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. PCT/US98/01789, filed on January 30, 1998. Claims which recite SapCDEF claims (14-17) or HIV (claim 5) are not afforded the earliest filing date as the provision Application does not provide original descriptive support for these claims.

Drawings

2. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.
3. Table 1 is cut off on page 18 and differs from Table 1 in the provisional Application.. Correction is requested.

Sequence Compliance

4. It was noted at page 7, line 15, a polynucleotide sequence is recited but no SEQ ID No was provided. At page 20, lines 28 and 29, amino acid sequences are recited, but no SEQ ID has been assigned. At page 23, lines 32, 34, 36 and 38 amino acid sequences of 4 amino acids or more are recited. At page 24, line 2,amino acid sequences of 4 amino acids or more are recited. Assignment of a SEQ ID NO is requested.

Incorporation by reference of essential material drawn to Claimed subject Matter

5. The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the

disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Specification

5. If applicant desires priority under 35 U.S.C. 119 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now patent no." should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

6. The first sentence of the specification does not refer to the priority documents upon which Application is based; amendment of the specification to reflect the foreign priority entitled to this Application is requested. A preliminary amendment directing the insertion of a sentence which sets forth applicant's claim to priority was not submitted.

7.

Claim Rejections - 35 U.S.C. § 101

8. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The claimed invention is directed to non-statutory subject matter. Claiming naturally occurring strains of bacteria is a non-statutory category of invention. The strains must show the hand of name. Claims 1,2,3,7 read in Campylobacter fetus strains which evidence natural recombination. Dworkin et al (1997) teach that Campylobacter fetus possess multiple partially homologous, (and therefore encode heterologous antigens) and highly conserved surface layer protein gene cassettes, tightly clustered in the genome and therefore, express heterologous antigenic determinants relative to other strains of Campylobacter fetus strains. Amendment of the claim 1 to clarify the mutant strain is not naturally occurring could obviate this rejection.

Claim Rejections - 35 U.S.C. § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1-17 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

It is apparent that the claimed *mutant strains of Campylobacter fetus* are required to practice the claimed invention. As a required element it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of the lines see 37 C.F.R. 1.802.

The specification does not provide a repeatable method for obtaining the *mutant strains* of Campylobacter and it does not appear to be a readily available material as no specific nucleic acid sequences which encode the heterologous protein antigens or therapeutic agents. Deposit of the *Campylobacter fetus strains* would satisfy the enablement requirements of 35 U.S.C. 112.

12. Claims 2,4,5,8, and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

13. Claim 2 recites the phrase "wherein a sapA homolog is altered. The word "homolog" lacks antecedent basis in claim 1 and therefore does not distinctly claim Applicant's invention.

14. Claim 4 recites the phrase "wherein the encoded S-layer protein represents a chimera between the native S-layer protein and the peptide encoded by the cassette." As an S-layer protein is not recited in claim 1, from which claim 3 depends, this phrase lacks antecedent basis in claim 1 and therefore does not distinctly claim Applicant's invention. Amendment to depend from claim 3 could obviate this rejection.

15. Claim 5 recites a Markush group of bacterial and viral pathogens, but no specific cassettes are defined. The claim appears to be claiming whole bacteria and therefore does not distinctly claim Applicant's invention. Amendment of the claim to recite clarifying language that define the specific heterologous antigen could add clarity.

16. Claim 8 recites a Markush group with two member contained therein. Claim 1 from which claim 8 depends recites that the protein is an antigen already but claim 8 defines the protein to be an antigen or a therapeutic agent. This is confusing in light of the limitations present in claim 1. Clarification of the members present in the Markush group is requested.

17. Claim 14 recites the use of SapCDEF genes. No nucleotide sequence is recited in the claims or in the instant specification. The claim is not defined in the specification and is therefore vague and indefinite.

18. Claims which recite abbreviations that have not been defined in the claims are unclear. The recitation of abbreviations in the claims is permitted upon the definition of the abbreviation in the claims.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

19. Claims 1-4, are rejected under 35 U.S.C. 102(b) as being anticipated by Fujita et al (December 1995).

Fujita et al (1995) disclose various strains which comprise sapA which encode DNA cassettes and express heterologous antigens, wherein the presence of non-conserved heterologous regions of the isolated mutant strains was identified through the lack of hybridation of a conserved sequence of sapA with the strains. (See table 1, page 445). The reference anticipates the now claimed invention.

20. Claims 1-3, 6-8 are rejected under 35 U.S.C. 102(a) as being anticipated by Dworkin et al (March 1996).

Dworkin et al disclose Campylobacter fetus strains which comprise mutations in S-layer protein, wherein the reference refers to the S-layer protein as (SLP's) and therefore would be encoded by sapA. The strains are taught to possess DNA cassettes that are mutated through rearrangement under the control of a single promoter and experience programed DNA inversion . Inherently the strains would evidence a 5' binding region and 3' secretion signal region with rearranged sequences between because strains of Campylobacter fetus mutant strains successfully avoid host immune defenses through rearrangement and presentation of different antigens to maintain viability in the host over a long period of time. Therefore, Dworkin anticipates the now claimed invention.

21. Claims 14-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Dworkin et al (June 1995).

Dworkin et al disclose the cloning of sapA and sapB nucleic acid sequences which encode recombinant sapA and sapB protein products. The expressed recombinant sapA and sapB products bound to Campylobacter fetus strains of homologous lipopolysaccharide (LPS) type, indicating that the conserved N-terminal was critical for LPS binding. The strains are taught to possess DNA cassettes that are mutated through rearrangement under the control of a single promoter and experience programed DNA inversion . Inherently the strains would evidence a 5' binding region and 3' secretion signal region with rearranged sequences between because strains of Campylobacter fetus mutant strains successfully avoid host immune defenses through

rearrangement and presentation of different antigens to maintain viability in the host over a long period of time. Therefore, Dworkin anticipates the now claimed invention.

22. Claims 1-4, 6-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Blaser (November 1994 or November 1993).

Blaser disclose mutant stains of Campylobacter fetus strains which comprise a heterologous protein inserted into the sapA gene. The strains are taught to possess DNA cassettes that are mutated through insertion of a nucleotide sequence which encodes kanamycin resistance, a known therapeutic agent. The mutant strains also comprise sapA DNA cassettes which comprise homologous and heterologous DNA which is the result of natural rearrangement caused by programed DNA inversion . Inherently the strains would evidence a 5' binding region and 3' secretion signal region with rearranged sequences between because strains of Campylobacter fetus mutant strains successfully avoid host immune defenses through rearrangement and presentation of different antigens to maintain viability in the host over a long period of time. Therefore, Blaser anticipates the now claimed invention.

Claim Rejections - 35 U.S.C. § 103

23. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

24. Claims 14 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blaser (1993) in view of Dworkin et al (1995) .

Blaser teaches the conservation of sapA homologs in Campylobacter fetus, a nucleic acid probe obtained through analysis of the N-terminal of a S-layer protein. The reference teaches the criticality of S-layer protein for virulence relative to significant veterinary and human pathogens and suggests the cloning of S-layer genes, the construction of mutant strains, production of a system for mutagenesis, the immunization of a host in order to obtain monoclonal antibodies and the use of an animal model to examine these reagents for their biological and biophysical applications but differs from the instantly claimed invention by failing to show a strain of bacteria modified to express SapCDEF genes and a method for immunizing a host with the strain.

Dworkin et al show the modification of E.coli through cloning of the genes that encode sapA gene and obtained recombinant plaques theat were immunoreactive with antibodies raised to Campylobacter fetus surface array protein in an analogous art for the purpose of constructing modified strains of bacterium that express C.fetus sapA genes in order obtain clones that express immunoreactive SapA protein for the study of Campylobacter genomic rearrangement as a means. of protein shift and antigenic variation during infection in vivo.

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the invention of Blaser in view of the teachings of Dworkin and immunize a host with a bacteria modified with SapCDEF genes because Dworkin teaches the

successful cloning of Campylobacter fetus sap genes which were expressed and were immunoreactive with antibodies raised to Campylobacter S-layer protein antigen and the person of ordinary skill in the art would have been motivated to obtain an immune response to the modified bacteria which contains the SapCDEF genes because Blaser teaches the importance of understanding the antigenic diversity of Campylobacter fetus S-protein layers as they are a critical virulence factor associated with disease and Blaser suggests the construction and use of modified bacteria to obtain antibodies to use in an animal model that provides insight into disease processes in order to answer questions of biological, biophysical and medical importance. In the absence of a showing of unexpected results, the applied references obviate the now claimed invention.

25. Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over of Blaser (1994 cited above.) in view Lubitz et al (US pat. 5,470,573).

See discussion of Blaser (1994) above. The reference teaches that Campylobacter fetus comprises S-layer protein and shows the construction of mutant strains that comprise a DNA cassette that encodes a heterologous antigen but differs from the instantly claimed invention by failing to show the use of a nucleic acid sequence that encodes a heterologous antigen from HIV.

Lubitz et al teach the construction of mutant strains of from gram negative bacteria that comprise S-layer proteins, in an analogous art for the purpose of producing mutant strains of bacteria that comprises a DNA cassette encoding a heterologous protein antigen, wherein the heterologous antigen may be encoded by nucleic acid sequences for antigenic structures for

human viruses, HIV (human immunodeficiency virus, HBV (hepatitis B virus and EBV (Epstein Barr virus) and other human proteins and antigens (col. 3, lines 16-24; (col. 2, lines 20-40).

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the invention of Blaser to include the nucleic acid sequence which encodes an antigenic HIV heterologous protein because Lubitz teaches that all gram negative bacteria, including Campylobacter, that produce S-layers are useful in the generation of mutant strains that encode a heterologous antigen, wherein the mutant strain would be used to stimulate an immune response in an animal through the administration of the mutant strain that expresses the heterologous antigen but is non-infectious and would not be a strain that would spread undesired pathogenic germs (col. 1, lines 47-49) but would express the heterologous antigen to a sufficient level to stimulate a strong immune response.

26. Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blaser (1994 cited above.) in view of Szostak et al (1996).

See discussion of Blaser (1994) above. The reference teaches that Campylobacter fetus comprises S-layer protein and shows the construction of mutant strains that comprise a DNA cassette that encodes a heterologous antigen but differs from the instantly claimed invention by failing to show the use of a nucleic acid sequence that encodes a heterologous antigen from HIV, SIV or animal pathogens.

Szostak et al (1996) is cited to show the use of S-layer proteins as a vehicle of foreign antigen presentation in an analogous art for the purpose of stimulating of an immune response in a

host against HIV and SIV and animal pathogens (see page 166, Table 2), as well as the construction of mutant strains that carrier viral antigens to obtain a vaccine composition to both bacterial or viral antigens by presenting a complex array of antigenic determinants to the immune system through the construction of mutant strains of from gram negative bacteria that comprise S-layer proteins, and a DNA cassette that encodes a heterologous antigen.

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the invention of Blaser to include the nucleic acid sequence which encodes an antigenic HIV heterologous protein because Lubitz teaches that all gram negative bacteria, including Campylobacter, that produce S-layers are useful in the generation of mutant strains that encode a heterologous antigen, wherein the mutant strain would be used to stimulate an immune response in an animal through the administration of the mutant strain that expresses the heterologous antigen but is non-infectious and would not be a strain that would spread undesired pathogenic germs (col. 1, lines 47-49) but would express the heterologous antigen to a sufficient level to stimulate a strong immune response.

Conclusion

27. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

28. Blaser ~~Wang~~ et al (1994) is cited to show that Campylobacter fetus possess multiple homologs of sapA and presents the phenomenon of surface layer protein variation at high frequency. The

ability to rapidly create novel surface layer proteins aids in the persistence of Campylobacter fetus viability.

29. Sleytr et al (1991) is cited to show the use of S-layer protein conjugates as carriers of immunogenic epitopes for the eliciting of antibodies and T-cell immune response.

30. Pace et al (1997) is cited to show vaccine compositions that comprises Campylobacter.

31.Dworkin et al (1993, abstract) is cited to show the cloning of the sapA2 gene into E.coli.

32.Blaser et al (1990) is cited to show surface array protein of Campylobacter fetus.

33. Salama et al (1995) is cited to show the genome map of Campylobacter fetus.

34. Boot et al (1996) is cited to show a microreview on the expression, secretion and antigenic variation of bacterial S-layer proteins.

35. Yang et al (1992, abstract) is cited to show the reattachment of surface array proteins to Campylobacter fetus cells.

36.Szostak et al (1997). is cited to show the use of S-layer proteins as a vehicle of foreign antigen presentation to a host for stimulation of an immune response.

37.Grogono-Thomas et al (1997) disclose mutant stains of Campylobacter fetus strains which comprise a heterologous protein inserted into the sapA gene

38.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner

can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be changing February 7, 1998. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp

April 18, 2000

James C. Housel 4/24/00

JAMES C. HOUSEL

SUPERVISORY PATENT EXAMINER